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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/701,871	11/05/2003	Renfeng Guo	UM-08443	6716

72960 7590 03/21/2008

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EXAMINER	
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ART UNIT	PAPER NUMBER
1645	

MAIL DATE	DELIVERY MODE
03/21/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/701,871	GUO ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/05/07*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26 and 27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO APPLICANTS' AMENDMENT

Applicants' Amendment

1) Acknowledgment is made of Applicants' amendment filed 12/05/07 in response to the non-final Office Action mailed 09/06/07.

Status of Claims

2) Claim 26 has been amended via the amendment filed 12/05/07.

Claims 26 and 27 are pending and are under examination.

Prior Citation of References

3) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Rejection(s) Withdrawn

4) The rejection of claims 26 and 27 that made in paragraph 10 of the Office Action mailed 09/06/07 under 35 U.S.C. § 112, first paragraph, as containing new matter, is withdrawn in light of Applicants' amendment to the base claim.

5) The rejection of claims 26 and 27 made in paragraph 11(a) of the Office Action mailed 09/06/07 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.

6) The rejection of claim 27 made in paragraph 11(b) of the Office Action mailed 09/06/07 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the base claim.

7) The rejection of claims 26 and 27 made in paragraph 12 of the Office Action mailed 09/06/07 under 35 U.S.C § 103(a) as being unpatentable over Riedemann *et al.* (*J. Clin. Invest.* 110: 101-108, July 2002 – Applicants' IDS) in view of Werfel *et al.* (*J. Immunol.* 157: 1729-1735, 1996, already of record) or Rothermel *et al.* (*Scand. J. Immunol.* 52: 401-410, 2000, already of record) and Behnke *et al.* (US 5,573,921, already of record), is withdrawn in light of the withdrawal of the new matter rejection.

New Rejection(s) Necessitated by Applicants' Amendment

Rejection(s) under 35 U.S.C. § 112, First Paragraph

(Scope of Enablement)

8) Claims 26 and 27 are rejected under 35 U.S.C § 112, first paragraph, because the specification, while being enabling for a method of treating CLP-induced sepsis in mice comprising administering to said mice an antibody including a monoclonal antibody which specifically binds C5a receptor and causes blockade of the C5a receptor wherein the mice's survival is prolonged, does not reasonably provide enablement for a method of treating sepsis in any generic subject suffering from sepsis, particularly gram positive sepsis, comprising providing a monoclonal antibody reagent that specifically binds to said C5a receptor and that is capable of blocking C5a receptor and administering the reagent to said subject wherein said subject's survival is prolonged, as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims.

The instant claims are evaluated based on the *Wands* analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability in the art; and
- The breadth of the claim.

The nature of the invention in the instant application pertains to a method of treating sepsis by prolonging survival in a subject suffering from Gram negative or Gram positive sepsis comprising administering a monoclonal antibody that specifically binds to C5a receptor (C5aR) and is capable of blocking C5a receptor. The administering step of the method claimed in the dependent claim 27 results in a decrease in symptoms of sepsis. Therefore, the therapeutic` outcome of the claimed method is prolongation of survival of the subject suffering

from sepsis. The limitation 'subject' encompasses a human and a non-human subject. The limitations 'gram-positive sepsis' and 'gram negative sepsis' encompass sepsis due to Gram positive and Gram negative bacilli, cocci, aerobes and anaerobes. The limitation 'gram positive sepsis' encompasses gram native bacterial sepsis and sepsis due to microbes other than Gram positive bacteria, such as, fungi. Section II of the instant specification describes how to produce monoclonal antibodies in mice by immunizing mice with C5aR peptide fragments via hybridoma. A further review of the instant specification indicates that Applicants used the mouse CLP model of sepsis. Figure 5 and Example 2 show that an anti-C5aR antibody, when administered to mice with CLP-induced sepsis prolonged the survival to 7 days after the CLP in 77% of the mice, whereas none of the mice treated with an irrelevant non-C5aR IgG survived beyond 5 days after the CLP. However, whether or not this sepsis model relates to or correlates with prolongation of survival in a human subject suffering from sepsis including Gram positive sepsis is not disclosed in the specification. A review of the state of the art on this issue indicates the following. The state of the art recognizes the CLP model to be a model of intra-abdominal sepsis that produces predominantly gram negative bacteremia and endotoxemia. See the sentence bridging pages 267 and 268 of Read *et al. J. Exp. Med.* 182: 267-272, 1995. A review of the state of the art further indicates the lack of predictability of the CLP sepsis model as therapeutically relevant in Gram positive sepsis. For instance, Hollenberg *et al.* (*Am. J. Respir. Crit. Care Med.* 164: 891-895, September 2001) taught that the CLP model of sepsis is an intra-abdominal sepsis model wherein the time course of mortality is similar to that seen in clinical septic shock. However, the applicability of the CLP model of sepsis to gram-positive sepsis is stated to be 'unproven'. See second full paragraph under 'Discussion' and the section 'Limitations' of Hollenberg *et al. Am. J. Respir. Crit. Care Med.* 164: 891-895, September 2001. The state of the art further teaches that because what kills patients may differ from what kills rodents, when the goal is to increase patient survival, one must remember that for a therapeutic agent to be clinically effective, it must treat what kills patients, and that the mortality rate of the preclinical model used to test a potential therapeutic agent should mimic the mortality rates of the patient populations in which it will be used. See Table 3 of Deitch EA. *Shock* 24: Suppl. 1, 19-23, 2005. Given this disclosure in the art, there is no predictability that the mouse CLP model of sepsis used in the

instant specification to test an anti-C5sRa antibody would bring about prolongation of survival and reduction in symptoms of sepsis in human patients suffering from sepsis, particularly Gram positive sepsis, upon administration of an anti-C5aR monoclonal antibody that is capable of blocking C5a receptor. Therefore, due to the lack of evidence and direction/guidance, and the lack of working examples and the evidentiary support enabling the full scope, the art-recognized unpredictability, the unproven relevance of the CLP sepsis model to Gram positive sepsis, the breadth of the claims, and the considerable quantity of experimentation necessary, undue experimentation would have been required by one of skill in the art to reproducibly practice the invention as claimed. The claims are viewed as not meeting the enablement provisions of 35 U.S.C § 112, first paragraph.

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

9) The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his/her invention.

10) Claims 26 and 27 are rejected under 35 U.S.C § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter, which Applicants regard as the invention.

(a) Claim 26 is vague and indefinite in the limitation: 'gram-positive sepsis' and 'gram-negative sepsis'. Is the sepsis gram-positive or gram-negative, or the element causing sepsis gram-positive or gram-negative? Are anaerobic microbes and fungi encompassed within the scope of the limitation 'gram positive'? Is endotoxemia excluded or included within the scope of 'gram-negative sepsis'? Clarification is requested.

(b) Claim 27, which depends from claim 26, is also rejected as being indefinite because of the indefiniteness identified above in the base claim.

Rejection(s) under 35 U.S.C. § 103

11) The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be

> patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 148 USPQ 459, that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or unobviousness.

12) Claims 26 and 27 are rejected under 35 U.S.C § 103(a) as being unpatentable over Huber-Lang *et al.* (*The FASEB J.* 16: 1567-1574, October 2002, already of record) in view of Werfel *et al.* (*J. Immunol.* 157: 1729-1735, 1996, already of record) or Rothermel *et al.* (*Scand. J. Immunol.* 52: 401-410, 2000, already of record) and Read *et al.* (*J. Exp. Med.* 182: 267-272, 1995).

Huber-Lang *et al.* taught a method of treating caecal ligation puncture (CLP)-induced sepsis in mice by providing a cyclic peptide antagonist reagent, C5aRa, to the C5a receptor (C5aR) and administering the reagent to the septic mice. The treatment not only diminished the C5a-dependent inflammatory lung injury symptom, but greatly improved or prolonged the mice survival. Huber-Lang *et al.* taught that C5aRa reagent blocks C5aR in sepsis. See abstract; pages 1567 and 1571; paragraph bridging page 1571 and 1572; and Figure 6. That the CLP-induced sepsis represents a model of intraabdominal sepsis producing Gram negative bacteremia and endotoxemia is impliedly disclosed in Huber-Lang *et al.* in light of what was well known in the art at the time of the invention. For example, Read *et al.* taught of the recognition in the art of CLP model of sepsis as a model of intraabdominal sepsis that produces predominantly Gram negative bacteremia and endotoxemia. See sentence bridging pages 267 and 268 of Read *et al.*

The method of Huber-Lang *et al.* differs from the instant invention in that the C5a receptor antagonist administered is not a monoclonal antibody antagonist reagent.

However, the monoclonal antibodies that bind specifically to C5a receptor (C5aR) were already known in the art at the time of the invention. For instance, Werfel *et al.* taught five anti-C5aR monoclonal antibodies. See abstract.

Similarly, Rothermel *et al.* taught the monoclonal antibody R63 that specifically binds to C5aR. See abstract; paragraph bridging the two columns on page 402 and on page 407; and paragraph bridging pages 403 and 404.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to replace the anti-C5aR antagonist in Huber-Lang's method with an alternative, already art-known anti-C5aR antagonist such as Werfel's or Rothermel's anti-C5aR monoclonal antibody antagonist, to produce the method of the instant invention with a reasonable expectation of success. Replacement of one art-known C5aR antagonist having specific binding ability to C5aR with another, alternative, art-known C5aR antagonist also having the C5aR-binding specificity was well within the realm of routine experimentation, would have been obvious to one of ordinary skill in the art, and would have brought about similar predictable results or effects.

Claims 26 and 27 are *prima facie* obvious over the prior art of record.

Remarks

13) Claims 26 and 27 stand rejected.

14) Applicants' amendment necessitated the new ground(s) of rejection presented in this Office Action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Central Fax number, (571) 273-8300, which receives transmissions 24 hours a day and 7 days a week.

16) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (in USA or CANADA) or 571-272-1000.

17) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's Supervisor, Shanon Foley, can be reached on (571) 272-0898.

/S. Devi, Ph.D./
Primary Examiner
Art Unit 1645

March, 2008